UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/029,574	12/20/2001	Per Sonne Holm	3961.002	4954

7590 07/01/2004

PENDORF & CUTLIFF
P.O. Box 20445
Tampa, FL 33622-0445

EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 07/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/029,574	HOLM ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/29/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *17-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/17/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Non-Final Rejection

Claims 1-20 are pending.

Election/Restrictions

Applicants' election with traverse of Group I (Claims 1-16) in Paper filed on 4/29/04 is acknowledged. The traversal is on the ground(s) that the examiner fails to show that examining all claims constitute a serious burden and applicant asserts that the claims of Group I and Group II concern the same essential invention because both are directed to replication of an E1-deificient adenovirus in a cell comprising YB-1 in its nucleus for the treatment of tumors, the groups only differ with respect to the source of YB-1. This is not found persuasive because as admitted by applicant the source of YB-1 is different for each method. The method in Group I requires transfecting a cell with an E1-deficient adenovirus comprising an YB-1 DNA sequence and expressing YB-1 in the cell and Group II does not require this method step. The method in Group I requires an E1-deficient adenovirus comprising an YB-1 DNA sequence and the method in Group II does not require the adenovirus. As stated in the election/restriction mails on 10/29/03, the search for each Group is not co-extensive and each group was classified in a different class/subclass. Other than applicants' assertion that the search for each group together will not be an undue burden on the examiner, the applicants have not provided sufficient evidence that it would not be an undue burden on the examiner to search both groups.

The requirement is still deemed proper and is therefore made FINAL.

Claims 17-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper filed on 4/29/04.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Information Disclosure Statement

The applicants state that search reports were included in the IDS filed on 4/17/02. However, there are no search reports of record. If applicants want the search reports to be considered, then the search reports should be included in response to this office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-9 and 12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 10 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treatment for tumors comprising administering to a tumor in a patient in need thereof said E1 deficient adenovirus comprising a DNA sequence encoding YB-1 and administration of substances which damage tumor cells, surgical tumor excision, radiation therapy, chemotherapy, and hyperthermia, does not reasonably provide enablement for a method of treatment for tumors comprising administering to a patient in need thereof a medicament comprising an E1-deficient adenovirus comprising a YB-1 encoding DNA sequence and gene therapy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 13-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for E1-independent replication of replication defective adenovirus comprising administering to a tumor cell in vitro a recombinant adenovirus carrying a DNA sequence encoding YB-1, inducing expression of YB-1 in said tumor cell, causing said adenovirus to replicate in the presence of YB-1, does not reasonably provide enablement for a method for E1-independent replication of replication defective adenovirus comprising administering to a cell recombinant adenovirus carrying a YB-1 encoding DNA sequence, inducing expression of YB-1 in said cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Applicants claim methods for treatment of tumors in a patent in need thereof, a method for E1 independent replication of a replication-defective adenovirus, wherein said methods use an E1 deficient adenovirus comprising a YB-1 encoding DNA sequence. In view of the guidance in the specification, the claimed methods are directed to a method of cancer gene therapy using the E1 deficient adenovirus.

At the time the application was filed, gene therapy was considered to be unpredictable due to significant problems in several areas. The state of the art, exemplified by Anderson et al., Nature, Vol. 392, pp. 25-30, 1998, displays major consideration for any gene transfer or any DNA therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,

2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method.

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several

major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2).

In further view of the doubts expressed above by Anderson and Verma, the state of the art for cancer gene therapy as discussed by Vile et al., (Gene Therapy, Vol. 7, pp. 2-8, 2000). Vile teaches:

> The problems which gene therapy for cancer will take into the next millennium focus far less on the choice of therapeutic gene(s) to be used than on the means of delivering them. There is already a battery of genes that we know are very effective in killing cells, if they can be expressed at the right site and at appropriate levels. None the less, until the perfect vector is developed, the choice of gene will remain crucially important in order to compensate for the deficiencies of the vectors we currently have available (page 2, 1st paragraph, left column). Whatever its mechanism, no single genes can be a serious contender unless it has a demonstrable bystander effect (page 2, right column). The requirement for such a bystander effect stems directly from the poor delivery efficiency provided by current vectors (page 2, right column).
>
> A genuine ability to target delivery systems to tumor cells distributed widely throughout the body of a patient would simultaneously increase real titers and efficacy. In truth, no such systemically targeted vectors exist yet. Injection of vectors into the bloodstream for the treatment of cancer requires not only that the vectors be targeted (to infect only tumor cells) but also that they by protected (from degradation, sequestration or immune attack) for long periods of time so that they can reach the appropriate sites for infection. Moreover, having reached such sites, the vectors must be able to penetrate into the tumor

> from the bloodstream before carrying out their targeted infection (page 4, bottom left column and top right column).

Thus, at the time the application was filed, the state of the art for gene therapy was considered highly unpredictable.

For additional reviews of the unpredictability of the gene therapy art, see Gomez-Navarro et al., European Journal of Cancer, Vol. 35, pp. 867-885, 1999; McNeish et al., Gene Therapy, pp. 1-7, 2004; Green et al., Cancer Gene Therapy, 9:1036-1042 2002; Alemany et al., Nature Biotechnology, 18:723-727, 2000; Gromeier, ASM News, 68:438-445, 2002.

With respect to the treatment methods in claims 7-12, the specification is only enabled for combination cancer therapy comprising administering said E1 deficient adenovirus comprising YB-1 encoding DNA sequence and administration of substances which damage tumor cells, surgical tumor excision, radiation therapy, chemotherapy, hyperthermia and not for the full breadth of the claimed method because it would have taken one skilled in the art an undue and excessive amount of experimentation to practice using an E1 deficient adenovirus by itself to treat a tumor in a patient. The art of record teaches that cancer gene therapy is unpredictable. The unpredictability taught by the art of record involves poor and inefficient delivery of adenovirus to target a tumor, host immune response which limit the ability of the adenovirus to infect a tumor, failure to efficiently infect certain tumors which lack adenoviral receptor CAR, promiscuous tropism which causes uncontrolled adenoviral infection and gene transfer into normal bystander cells, uptake intake into the liver of adenovirus instead of uptake into target tumor when the virus is systemically (e.g., intravenous administration) delivered to a patient.

With regard to previous experience with adenovirus to treat cancer, McNeish et al., (supra) teaches that in 93 patients receiving adenoviral particles, no objective clinical response were seen patients receiving the virus alone but that some responses were seen in patients receiving the virus in combination with chemotherapeutic agents. McNeish further teaches that:

Although targeting tumor suppressor gene pathways is an attractive and logical strategy for cancer gene therapy, results from clinical trials have not mirrored the preclinical studies. Clearly, the ability to induce cell cycle arrest and apoptosis in vitro or growth arrest in mouse xenografts does not guarantee response in clinical trials. See page 5.

This is further supported by Gomes-Navarro et al., (supra), who teaches that, "the spontaneous behavior of human tumors is somewhat different for that of malignant cells in vitro, and from that of experimental tumors in animal models."

Applicants provide no working example of the methods set forth in claims 7-12. The applicants teach that an E1 minus adenovirus coding for YB-1 can kill tumor cells in vitro; however, the art of record and the specification do not teach one skilled in the art how to correlate between results obtained in vitro studies set forth in the specification with results which the skilled artisan would reasonably expect to see in vivo. Furthermore, oncolysis in a cell line does not provide a nexus to treatment of tumors in vivo because the art of record and the specification do not provide sufficient guidance and/or factual evidence that killing tumor cells in vitro reasonably extrapolates to treatment of a tumor in vivo because killing tumor cells in vitro does not indicate that the number of tumor cells killed in a tumor in vivo is more than the number of new tumor cells in the tumor.

Furthermore, with respect to claim 10 directed to using additional therapy with the claimed E1 deficient adenovirus, the specification provides sufficient guidance for a method of treating a tumor in a patient comprising administering said E1 deficient adenovirus comprising

YB-1 encoding DNA sequence and administration of substances which damage tumor cells, surgical tumor excision, radiation therapy, chemotherapy, and hyperthermia because the additional methods listed in claim 10 were already known in the art, at the time the application was filed, for treating a tumor in a patient. In addition, the specification and the art of record do not provide sufficient guidance and/or factual evidence that the claimed adenovirus would counteract the additional therapies set forth in claim 10. However, claim 10 reads on using gene therapy in combination with the claimed E1 deficient adenovirus. The art of record and the specification are absent for using gene therapy in the claimed method. The relevance of using gene therapy is unclear because neither the applicants nor the prior art teach a nexus between using the claimed method and using gene therapy in the claimed method.

Given the above analysis of the factors, it is concluded that the specification provides sufficient guidance for combination therapy comprising administering said E1 deficient adenovirus comprising YB-1 encoding DNA sequence and administration of substances which damage tumor cells, surgical tumor excision, radiation therapy, chemotherapy, and hyperthermia and not for the full scope of the claimed invention.

Furthermore, with respect to claims 13-16, the claims can read on a method for E1-independent replication of a replication defective adenovirus in vitro or in vivo. With regard to the claimed method practiced in vitro, applicants' disclosure does teach one skilled in the art how to use this method on tumor cells in vitro. The in vitro embodiments involve transfecting of immortalized cells with the adenovirus showing nucleus location of YB-1 using E1-deficient adenovirus encoding YB-1 DNA sequence; showing oncolysis of tumor cell lines by adenovirus expressing YB-1; and showing formation of adenoviral particles in a cancer cell line.

In addition, with respect to using the claimed methods in vivo, the only disclosed use for in vivo is for treatment of tumors, cancers, malignant diseases, cells and tissues exhibiting aberrant growth. For the reasons set forth above, the claimed in vivo method is not considered enabled. For the unpredictability of cancer gene therapy see Vile (supra), Green (supra) and Gomes-Navarro (supra). Applicants provide no working example of the in vivo method embraced in claims 13-16. The applicants teach that an E1 minus adenovirus coding for YB-1 can kill tumor cells in vitro. In view of the In Re Wands Factors, one skilled in the art could correlate not from the results obtained from the in vitro studies to killing tumor cells in vivo using administration of the claimed adenovirus. In addition, the specification does not teach how to overcome the problems taught by the art of record with adenovirus gene therapy and using any route of administration. Therefore, it would take one skilled in the art an undue amount of experimentation to determine what route of administration (*e.g.* intravenous, dermal, nasal, rectal, vaginal, inhalation, or topical administration) would result in oncolysis of a tumor cell in vivo using the claimed methods.

In conclusion, the as-filed specification and the claims coupled with the art of record, at the time the invention was made, only provide sufficient guidance and/or evidence to reasonably enable a method for E1-independent replication of replication defective adenovirus comprising administering to a tumor cell in vitro a recombinant adenovirus carrying a DNA sequence encoding YB-1, inducing expression of YB-1 in said tumor cell, causing said adenovirus to replicate in the presence of YB-1 and not for the full breadth of the claimed invention. Given that cancer gene therapy wherein an adenovirus is employed to treat a tumor in an individual was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to

a cancer gene therapy effect produced by any adenovirus cited in the claims, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicants' disclosure and the unpredictability of cancer gene therapy.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (f) he did not himself invent the subject matter sought to be patented.

Claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 11 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter. U.S. application 10/451,210 has one common inventor with the instant application. In addition, at the time the instant application was examined there was no evidence of record that the application and US 10/451,210 were commonly assigned.

Claims 1-6 are directed to an E1-deficient adenovirus comprising a DNA sequence encoding a YB-1 protein. US '210 claims an adenoviral nucleic acid comprising a nucleic acid sequence coding for YB-1, wherein the adenoviral nucleic acid is E1 deficient (claim 53). El deficient means that the adenovirus is E1a and E1b deficient. US '210 claims an adenovirus comprising the adenoviral nucleic acid (claim 65).

Claims 7-11 embrace using combination therapy comprising administering said E1 deficient adenovirus comprising a DNA sequence encoding YB-1 and administration of substances which damage tumor cells, surgical tumor excision, radiation therapy, chemotherapy,

and hyperthermia. US '210 claims using a cyostatic agent with the adenovirus to treat a tumor disease (claims 68, 70, and 71).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 11 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 53, 65, 68, 69, 70, 71, 72, and 79 of copending Application No. 10/451,210. Although the conflicting claims are not identical, they are not patentably distinct from each other because the pending application and application '210 are directed to an adenoviral nucleic acid comprising a nucleic acid sequence coding for YB-1, wherein the adenoviral nucleic acid is E1 deficient. In addition, US '210 claims using a pharmaceutical comprising a cyostatic agent with the adenovirus to treat a tumor disease (claim 71).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, SPE - Art Unit 1635, can be reached at (571) 272-0760.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600